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Abstract

This paper summarizes numerous conceptual and experimental advances over the past two decades in the study of hormesis. Hormesis is now generally accepted as a real and reproducible biological phenomenon, being highly generalized and independent of biological model, endpoint measured and chemical class/physical stressor. The quantitative features of the hormetic dose response are generally highly consistent, regardless of the model and mechanism, and represent a quantitative index of biological plasticity at multiple levels of biological organization. The hormetic dose-response model has been demonstrated to make far more accurate predictions of responses in low dose zones than either the threshold or linear at low dose models. Numerous therapeutic agents widely used by humans are based on the hormetic dose response and its low dose stimulatory characteristics. It is expected that as low dose responses come to dominate toxicological research that risk assessment practices will incorporate hormetic concepts in the standard setting process.

Keywords

hormesis, hormetic, biphasic, U-shaped, adaptive response, inverted U-shaped

Introduction

This paper discusses insights that have been gained as a result of assessing the concept of hormesis since approximately 1990. Of the two dozen new findings and ideas that will be discussed in this paper, essentially all were unexpected. Of particular surprise was that prolonged and detailed assessment of the nature of the dose response, especially in the low dose zone, would provide important and basic conceptual insights that have relevance to all biological systems. Thus, while the plan was to assess hormesis, the journey has yielded far more than was anticipated. Each discovery/insight is briefly described and referenced. It is hoped that the reader will be intrigued by the range of biological insights that studying the hormesis concept has revealed. Furthermore, this paper will provide a useful and concise summary of the current status of hormesis-related research as well as insights into possible future developments.

Critical failure of public health regulatory agencies to validate the threshold dose-response model in the 20th century

The threshold dose-response model is fundamental to all aspects of biology that use dose-response relationships. This model has been central to toxicology, pharmacology and public health regulatory agencies since the 1930s, affecting chemical/drug safety evaluations, modern risk assessment practices and public health exposure standards. The study and application

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of the threshold dose-response model is therefore central to the fields of toxicology, pharmacology and risk assessment.[1-3]

This centrality of the threshold dose-response model within the biomedical sciences and public health regulatory agencies has lead to the assumption that this dose-response model has been studied in detail, scientifically vetted and validated, and can be reliably assumed to provide accurate estimates of biological responses especially in the low dose zone (i.e. below toxicological and pharmacological thresholds). In the course of our assessment of hormetic dose-response relationships, the question was raised as to whether the threshold dose response was formally assessed for its capacity to predict below threshold responses. While there was the general belief that it must have been, given the importance of this question and the universal acceptance of this model within the scientific and regulatory communities, our comprehensive attempts to find research that had addressed this issue uniformly failed. Yet, this failure was very unsettling, for how could the biomedical community have built an entire toxicological and drug testing and regulatory framework upon a dose-response model that had not been validated? This seemed to be implausible and therefore could not possibly be true. It most likely meant that our comprehensive attempts were not really 'comprehensive' and that we must have been missing the obvious. Yet, renewed attempts with differing search strategies to ferret out the scientific vetting of the threshold dose-response model continued to fail to yield any relevant publications. Eventually a disturbing conclusion was reached, that is, the principal dose-response model upon which chemical and drug toxicity testing has been based had never been validated, but simply accepted as true, being passed down with authoritative conclusionary statements from textbook to textbook, from professor to student, from regulatory agencies to citizens, across generations of scientists, creating an illusion of knowledge and informed guidance.

This situation led to two avenues of further inquiry. The first was the need to develop an historical reconstruction of the threshold dose-response concept that would have lead to how this 'blind' acceptance without validation and vetting occurred (see ref 4 for a detailed assessment). The second critical issue was the need to test predictions of the threshold dose-response model in large data sets using a priori entry and evaluative criteria.[5-9] That is, we would conduct our own vetting of the threshold dose-response model to make accurate predictions of responses below the threshold. These studies have documented that the threshold dose response very poorly predicts responses below the estimated threshold, a performance that was broadly generalizable. This failure of the threshold model to make accurate predictions of responses below the threshold in the above published data was also consistent with the publication of a large number of studies within the hormesis database[10,11] that are supportive of the hormesis dose response and not the threshold model.

These findings point to a critical and ongoing failure of the scientific and regulatory communities to properly validate models, especially ones that are directly used to affect public health and medical practices. The societal costs of the failure to vet and validate the threshold dose-response model for the past 75 years are unknown. However, one must ask how it was possible for U.S. federal agencies such as the EPA, FDA, ATSDR, NIEHS, NIOSH, OSHA and others to never conduct or fund studies that would have addressed this question. The same question may be asked of private sector funding of toxicological and pharmaceutical research and why this question has never been addressed.

It should be noted that the FDA did recognize the need to validate linearity at low dose predictions in the mid-1970s, with the mega-mouse testing of the carcinogen 2-AAF. However, this effort revealed that risks lower than 1/100 were not practically achievable for carcinogens within chronic animal bioassays. The failure of the study to adequately test linearity at low dose modeling, despite the use of enormous resources (e.g. 24,000 animals), lead to a continued reliance on non-validated models for risk assessment of chemical carcinogens. An important irony was that a detailed analysis of the FDA/2-AAF study by an expert panel of the US Society of Toxicology revealed an unequivocal hormetic dose response for bladder cancer, with risks decreasing below the control group at low doses.[12]

Hormesis: it is real and common

When the BELLE Advisory Committee was first organizing, there was no generally accepted position on what was the status of hormesis within the scientific community. However, there were considerable questions over whether it was a real, reproducible phenomenon. Its status within the scientific community in the late 1980s and early 1990s was marginal

at best. In fact, from 1945–1989, the Web of Science reports only 159 cumulative citations using the terms hormesis or hormetic, all appearing from 1982 onward. The hormesis concept had therefore been explored only to a very limited degree through the 1980s. In contrast, in the year 2009 alone, the number reached 2460. So, the question maybe asked as to how hormesis emerged from an uncertain and marginalized concept to one that became accepted as real?

The key initial activity derived from a desire of the Texas Institute for Advanced Chemical Technologies (TIACT) based at Texas A&M University to determine whether hormesis was real or not. More specially, Dr Paul Deisler, a board member of TIACT, wanted TIACT to fund a study to answer this question. His idea led to a grant being given to the University of Massachusetts in 1995. It was the TIACT funding that lead us to create objective evaluative criteria to assess the existence of hormetic dose responses and to the conclusion that hormesis was not only a real and reproducible phenomenon but that is was likely to be very general, being independent of biological model, endpoint measured and chemical class/physical stressor agent.[13] This research has continued to the present with a progressively expanding database of findings of hormetic dose responses.[10,11] Specialized studies have been published on numerous receptor systems,[14-22] chemotherapeutic agents,[23] ethanol,[24] inorganic agents,[25] immune responses,[26] human tumor cell lines,[27] numerous neuroscience endpoints,[28-41] plant biology[11] amongst others. These findings have added more support to the conclusion that the hormetic dose response is highly generalizable with broad-based applications.

Development of a frequency of hormesis

Even though the above discussed research indicated that hormesis was real and a very general phenomenon, it did not provide a measure of the frequency of hormesis in the toxicological and/or pharmacological literature. Estimating the frequency of hormesis was considered to be of importance for regulatory agencies. For example, different strategies or policies could be developed if the hormetic frequency was <5% versus >40%. Thus, just knowing that hormesis was a real biological phenomenon was insufficient. This lead to an evaluation of nearly 21,000 articles in three toxicology and/or pharmacology journals from their inception to the most recent, assessing all articles with a priori entry and evaluative criteria. It is interesting to note that only 2% of the dose responses satisfied the entry criteria but of those that did, nearly 40% satisfied the evaluative criteria for hormesis.[5] Thus, for the first time, there was documentation of a frequency of hormesis within the published literature.

Comparing the threshold, linearity at low dose and hormesis models: which is most frequent?

In general, our research has focused on comparing the hormetic dose response with the threshold dose response for frequency. This is because the endpoints that had been studied in the most appropriate manner (i.e. strongest study designs) have involved non-cancer endpoints. This fact has lead to giving the linear model less emphasis in our publications. In these comparisons, the most striking observation is that the threshold dose-response model consistently performs very poorly. This has been shown in multiple studies using a wide range of biological models, endpoints and agents.[5-9] In contrast, the hormetic model has performed very well in these same head-to-head comparisons. However, recently there has been the proposal that all agents may induce their toxic effects via a linear, non-threshold manner.[42] In our studies that are cited above in this section, it was found that the linear at low dose model, like the threshold dose-response model, performed very poorly in our evaluations, thereby not supporting this new attempt to generalize the linear model.

Defining hormesis

In a broad reading of the general or popularized articles on hormesis, it has often been defined as a low dose beneficial response to a stressor agent. However, Calabrese and Baldwin[43] proposed that the dose response definition of hormesis be decoupled from a decision on whether the response was beneficial or not. This was done because it had become obvious to us that the low dose hormetic stimulation could be either beneficial or harmful, depending on the situation. For example, an antibiotic such as streptomycin may stimulate the proliferation of harmful bacteria in an animal while killing the bacteria at higher doses. Thus, at low doses, the streptomycin would be helping the bacteria but harmful to the patient while the reverse would be the case at higher doses. A chemical

may be seen to display an enhancement of longevity at low doses but decreasing longevity at higher doses. However, whether the increase in longevity for the individual would be beneficial for the species may not be true. Thus, the decision on whether the low dose hormetic response is beneficial or not can be complex and not necessarily immediately obvious.

Quantitative features of the hormetic dose response

When we initiated research on hormetic dose responses, we did not provide overriding consideration to the quantitative features of the dose response. Our thinking was far more qualitative at the early stages of development, that is, was there a low dose stimulation and was it reproducible. However, once data emerged on several thousand hormetic dose responses that were assessed for various dose-response parameters, it became clear that the most consistent quantitative feature of the hormetic dose response was the magnitude of the stimulatory response. Rarely was it greater than twice the control group. In general, the maximum stimulation for hormetic responses appears to be 30%–60% greater than control group.[44] This feature was consistent across biological models, endpoints and agents tested. This was an important observation since it clarified why hormesis could be difficult to document. That is, since the maximum stimulation was modest, it would require the use of rigorous study designs along with considerable statistical power.

With respect to the width of the stimulatory response, this was generally modest as well, typically being about a factor of 10. However, in about 2% of the cases, the width of the stimulatory zone was quite wide, exceeding a factor of 1000.[3] These observations have considerable toxicological and clinical implications as one considers the therapeutic zone or zones of exposure to avoid.

Another feature of the hormetic dose response curve is that it was always adjacent to the threshold response. This characteristic would make the upper boundary of the hormetic response very predictable, a factor that could be of considerable value to those involved with risk assessment and therapeutics.

Is there a single mechanism for hormesis?

This has been a common question raised at various conferences held on the topic of hormesis. When one considers that the hormesis phenomenon is extremely general, being independent of biological model, endpoint, and chemical class, it quickly becomes clear that a single proximate mechanism is not possible to account for the diversity of hormetic dose responses. However, there appears to be a common overall strategy of resource allocation within all biological systems, regardless of endpoint measured. The hormetic dose response may quantify how the system allocates resources. This is reflected in the observation that the maximum stimulatory response is typically limited to only 30%–60% greater than the control group.

General hormetic mechanisms: direct stimulation and overcompensation stimulation

Another issue that was not considered in the early evaluative stages of the hormesis concept was whether it occurred via a direct stimulation or via compensatory response. However, this would become an important consideration as will be seen below. My first research experience introduced me to the concept of hormesis, but I was unaware of the term or its temporal qualities. I observed that a synthetic growth inhibitor consistently induced a biphasic dose response for growth in Peppermint with a low dose stimulation and a high dose inhibition.[45] Although plant growth was measured weekly, the results of greatest interest were those at the end of the study, which was typically about 6 weeks. More than two decades later, I read several papers by Tony Stebbing on hormesis that emphasized the importance of the dose-time response in assessing hormesis.[46] He indicated that initially there would be a disruption in homeostasis (i.e. toxicity), followed by an overcompensatory response that would be seen as a stimulation. This encouraged me to go back to my original laboratory notebooks, re-analyzing the data in the manner suggested by Stebbing. When this was completed, Stebbing's prediction was confirmed. That is, during the initial weeks of the study, there was a dose-dependent decrease in growth followed by the overcompensation growth stimulation.[47] This re-assessment was possible because the study design employed many doses and a repeated measures component. The majority of experiments do not include both components, thereby preventing a detailed dose-time response. In the hormesis database,[10,11] about 20% of experiments have a dose-time relationship. These experiments have been important in

clarifying that hormetic dose responses may occur via the overcompensation stimulation mechanism. However, we also observed that there were numerous reliable examples in which hormetic dose responses occurred as a result of a direct stimulation, with no initial disruption in homeostasis.

These observations were interesting because they indicated that hormesis could occur by two different modes of action. Despite this clear difference in mechanism, the quantitative features of hormetic dose responses were the same for the direct and the overcompensation stimulation types of hormesis. Since most studies demonstrating hormesis do not contain a time component, one is not able to know whether the particular case of hormesis is direct stimulation or overcompensation. The question was raised (and will be addressed later) as to why these two types of hormesis would also display the same quantitative features of the dose-response relationship even though they were affected via different mechanisms.

An hormetic mechanism strategy

A wide range of drugs has been found to reduce anxiety in rodents by activating one of a variety of specific receptor pathways. Regardless of the drug used and the pathway activated, the quantitative features of the dose responses are similar. Another interesting feature is that the co-administration of anti-anxiety drugs that act via different mechanisms (i.e. activate different receptor pathways leading to the decrease in anxiety), regardless of drug potency, have their combined responses limited by the constraints of the hormetic maxima (i.e. plasticity constraints). This suggests that there is a downstream integration of multiple pathways, each of which can facilitate a reduction in anxiety. This downstream integration/conversion suggests a type of carousel model in with the resulting molecular product, that is, the dose response (e.g. analogous to the speed of the carousel) being similar.

High risk groups

The issue of high risk groups and how they are protected by environmental health standards is an important public health consideration. In 2001, we were challenged by Lave[48] to explore this issue since our earlier publications of hormesis had been directed to other questions. In a 2002 paper, Calabrese and Baldwin[49] reported that hormetic dose responses were found to be generally independent of inherent susceptibility. The principal finding was that those at increased risk have their dose response shifted to the left, showing hormesis and toxicity at lower doses than the so-called normal segment of the population. However, in some cases, the susceptible segment of the population is at high risk precisely because it lacks the adaptive hormetic mechanism. Furthermore, the quantitative features of the dose response for those at increased risk are similar to the normal segment of the population. The knowledge of hormesis and differential susceptibility is important for those involved in setting environmental and occupational exposure standards as well as for the pharmaceutical industry, which may target the hormetic stimulation when defining the therapeutic zone or when the hormetic zone needs to be avoided due to toxicity concerns.

Toxicological/pharmacological potency

Agents can widely differ in their potency for producing the same endpoint. Such differences could exceed several orders of magnitude. However, despite such differences in potency, there is no difference amongst these agents with respect to the quantitative features of the hormetic dose response nor other qualities of the hormetic response.[3] This is an important concept since a very potent agent will display the same quantitative features of the hormetic dose response as a weak agent, but doing so at a far lower dose.

Mixtures and hormesis

Mixtures have not been extensively studied within an hormetic context. However, there are sufficient data published that permits one to make some tentative general conclusions on how they are handled within an hormetic framework.[50] Particularly insightful have been the studies of Flood and his colleagues[51-54] concerning the effects of drugs on memory in rodents. These investigators have consistently shown a complex dose-response relationship. Most importantly, the maximum extent to which they could increase memory was constrained by the so-called 30%–60% stimulation rule. This was the case regardless of whether one or multiple agents were administered. If two or more memory-enhancing drugs were administered, there could be an additive or greater than additive relationship, but this would have to occur at a very low dose, where the response was some distance below the 30%–60% physiological performance cap. As the response approaches the maximum, the nature of the interaction would change from greater

than to less than additive. In effect, the nature of the hormetic interaction is principally seen at the level of dose rather than response. These findings indicate that the stimulatory response will be limited to the 30%–60% zone but that it may be possible to achieve this response level with a considerably lower dose due to the chemical interaction. Flood indicated that this would reduce the likelihood of experiencing adverse side effects. The concept of mixture responses within an hormetic dose response context is considerably different than that which is typically studied within a toxicological framework. The hormetic interaction has important response constraints, whereas this is not the case for standard toxicity endpoints at doses greater than the threshold.

Hormesis: a quantitative index of biological plasticity

The most striking feature of hormesis is that the stimulatory response is consistently modest with the maximum response about 30%–60% greater than the control value. Since this is the case regardless of mechanism, endpoint and model, pharmacological potency, for mixture responses and for chemical class, it strongly suggests that this response describes the plasticity of biological systems at multiple levels of organization ranging from the cell to the organ to the organism.[55,56] The findings indicate that this biological response is highly conserved as it is seen from organisms ranging from bacteria to man as well as in plants. These findings have important implications for clinical therapeutics as well as all dimensions of biological performance.

Preconditioning is a manifestation of hormesis

The term preconditioning entered the medical lexicon in 1986 when Murry et al.[57] reported that a brief occlusion of the coronary artery of dogs 1 day prior to inducing a major myocardial infarction reduced cardiac damage by about 80% as compared to the control group in which only the myocardial infarction was induced. These findings initiated a cascade of research, which was generalized well beyond the cardiac system, yielding similar protective findings. While most of these studies used only one or two types of exposures making it impossible to assess an hormetic explanation, a number of studies have teased out the dose response of the conditioning agent/exposure regiment.[58,59] In these studies, the conditioning agent displays an hormetic biphasic dose response, with similar quantitative features of hormesis. The findings clearly indicate that there is an exposure optima with the protection dropping off on either side. If the preconditioning exposure is too high, then it could further enhance the toxicity of the subsequent toxic or harmful exposure/treatment.

Hormesis and the 21st century

In an earlier question/answer, it was noted that the vast majority of papers reporting hormetic dose responses are recent, occurring since the year 2000. One major reason for this is that in the mid-1980s, there was a major shift toward the use of cell culture and the study of cell lines. The use of cell cultures often has employed 96 cell plates that allow for the assessment of 7–11 concentrations in each experiment. This is 2–3 times more treatment groups than the typical in vivo rodent assay. This was what the hormesis concept required in order to increase the likelihood of it being observed. In 2007, the US National Academy of Sciences (NAS)[60] published a book concerning toxicity testing for the 21st century. Amongst their far reaching recommendations was the eventual elimination of the chronic bioassay and its replacement with well-validated in vitro studies using various human cell lines. If these recommendations are followed it suggests that hormetic dose responses will be a central feature of 21st century toxicological findings[60] as in vitro studies will often employ a larger number of treatment groups across a broader concentration range than would occur with a traditional in vivo toxicological study.

Hormesis and biological performance

The hormetic low dose stimulatory response represents a new concept in toxicology and pharmacology, being a measure of biological performance. This is seen with respect to endpoints such as plant growth, strengthening bones, improving memory, decreasing anxiety, increasing seizure thresholds, growing hair, attracting neutrophils to sites of infection, decreasing mutation rate and tumor formation and many other responses. The dose response therefore has two response components, that is, the above the threshold response and the below the threshold response. The above threshold response is generally unrestrained as seen with high dose toxicology in which evidence of tissue damage or mutational effects or other toxic

endpoints can increase by several hundred or even a thousand or more fold. While there are often pharmacokinetic limits on the induction of toxicity, toxic responses are generally very progressive and have the potential to massively increase. This is not the case with responses below the threshold where the hormetic stimulation becomes manifest.

Drug benefit limitations

When a new and improved drug reaches the market, there maybe the assumption that it will produce a greater benefit than older competitive drugs. It will grow more hair, reduce anxiety better, make stronger bones and boost memory. The hormesis concept indicates that this is not necessarily the case. Hormesis imparts a limit on how much gain there is in the biological system. Many hundreds of endpoints display the same approximate level of modest maximum gain, that is, only in the 30%–60% range. Even the vastly more potent drugs will not increase the performance. They simply give the same performance, but at a lower dose. The gain in the system is limited by the constraints imposed by plasticity.

Is hormesis related to homeopathy?

In earlier writings, I have separated hormesis from homeopathy. I even went so far as to say that homeopathy was the equivalent of a scarlet letter on the forehead of hormesis.[61] The lay public and even many in the medical profession often confusedly merged the concepts. Hugo Schulz discovered the basic concept of hormesis in the mid-1880s in experiments assessing the effects of disinfectants on the metabolism of yeast. Through a type of convoluted logic, Schulz came to believe that he had discovered the explanatory principle of homeopathy. In fact, the studies of Schulz had nothing to do with the concept of homeopathy. However, biomedical investigators in The Netherlands[62,63] have tried to explicitly design studies that might link the two concepts via what is now called postconditioning hormesis.[64] These investigators demonstrated that low doses of heat or chemical toxin when given after a stress (i.e., disease process simulation) can amplify the initial response to stress in a hormetic-like fashion. While this research was experimental rather than clinical, it provides a framework for further study. Given legitimate criticisms of the ultra dilutionist wing of homeopathy, it must be emphasized that this research of Van Wijk deals with exposure to stressor agents that can be readily measured and is fully capable of being evaluated within normal biomedical experimental protocols. Unfortunately, this research was published during the mid-to-late 1990s and has not been continued. Nonetheless, this new experimental framework provides a conceptual vehicle to facilitate the evaluation of some homeopathic treatment strategies within an hormetic context.

Hormesis and harmful effects

When I first started to assess hormetic dose responses, little thought was given to the possibility that harmful effects would occur. Most attention was given to whether hormesis was a real, reproducible phenomenon. However, it eventually emerged that the low dose stimulatory hormetic responses could at times lead to undesirable effects. For example, low doses of antibiotics were shown to occur as early as the mid-1940s by FDA researchers to stimulate the proliferation of harmful bacteria. In vivo studies with low doses of penicillin as well as streptomycin enhanced mortality in mice given an LD_{50} dose of a deadly bacterial strain while preventing death at higher doses.[65,66] This remains a potentially very significant area of public health research.

Low doses of numerous agents, including anti-tumor drugs, have been shown to enhance the proliferation of tumor cells.[27] These findings suggest that under certain conditions, the administration of anti-tumor drugs to cancer patients may enhance the proliferation of the tumor cells. This is particularly the case for drugs with a long biological half-life. Some anti-tumor drugs used for the treatment of humans, such as the drug suramin, not only display the hormetic biphasic dose response with multiple tumor cell types but also have a rather prolonged period of residence within the human body, taking nearly 2 months to clear.[67] In such cases, there would be a prolonged period of time during which the drug would be present at very low concentrations. Whether these concentrations would be optimized to enhance tumor cell proliferation is an important question to resolve. The fact that anti-tumor agents can stimulate tumor cell proliferation at low doses within an hormetic context has generally not been widely appreciated by the cancer treatment community that emphasizes the high-dose killing portion of the dose-response curve.

This concept has been generalized to other areas of cancer treatment, including brain tumors. For example, anti-inflammatory agents such as dexamethesone

have been shown to enhance the proliferation of human neuroepithelial brain cancer cells in vitro displaying an hormetic dose response.[68-71] Such findings generated considerable concern amongst brain surgeons who commonly used anti-inflammatory agents in the management of their patients' pain.

Another potential adverse effect caused by the low dose hormetic stimulation may include the enlargement of the prostate gland due to the proliferation of smooth muscles following exposure to cardiac glycosides.[72,73] The magnitude of stimulation, which is about 20%–40%, is likely to have clinical implications in some patients with respect to affecting urination. The condition known as Dupuyteren's Contracture is also likely due to the overproduction of fibroblasts induced by low doses of reactive oxygen, with the response following an hormetic dose-response relationship.[74]

A number of immune diseases have also been related to the occurrence of a low dose stimulatory response. While a detailed assessment of hormetic responses of the immune system suggested that most would be beneficial, in about 20% of the cases, the low dose stimulatory response could lead to harmful effects, such as certain autoimmune responses including lupus[75] and tuberculin hypersensitivity.[76]

Hormesis in drug discovery, development and in the clinical trial

Drug discovery, development and clinical trial efficiency could be significantly enhanced if they were guided by principles derived from an understanding of the concept of hormesis. This is the case for drugs designed to kill harmful agents. For example, in screening of agents that may be very effective at killing bacteria, fungi, viruses, yeasts and tumor cells, it would also be important to know whether these agents might be effective stimulating the proliferation of these organisms. It would also be important to know the biological half life of the drug in humans. Ideally, the drug should be effective in killing the harmful agent, have a low capacity to induce cell proliferation at low doses and have a short biological half-life. Nascarella and Calabrese[77] have recently demonstrated that there is an inverse relationship between the capacity to kill yeast cells that are models of human tumor cells and the capacity to induce an hormetic dose response. This makes it even more important to be guided by hormetic principles in the selection of anti-tumor cells. It would be important to know whether this concept could be generalized to the case for harmful bacteria, yeasts and viruses.

The concept of hormesis is central to drug development when the goal of the research is to determine whether the drug can increase human performance (e.g. memory enhancement, bone strengthening). The quantitative features of hormesis will determine the magnitude of the enhanced performance as well as the width of the therapeutic zone. However, it is also doubtful that researchers in these areas are acquainted with the hormesis term, its concept and implications. Of particular concern is how the hormetic concept can guide and affect response expectations, study design and statistical power features of both preclinical studies and clinical trials.

Is the hormetic response more dependent on the organism or the inducing agent?

The question has often been asked as to whether all chemicals can induce hormesis or conversely is the key determinant of the hormetic response the organism. Since all chemicals can induce toxicity, depending on the dose, and hormesis may occur as an overcompensation to a disruption in homeostasis, hormesis would be expected to occur for all agents depending on the experimental context. On the other hand, this is not likely to be the case for agents that induce hormesis via a direct stimulation since these agents are typically going to occur via a receptor-mediated pathway activation process.

Chemical structure and hormesis

The chemical structural determinants of hormesis is a generally unexplored area of investigation. Nonetheless, several groups have reported that structural factors can be determinants of whether an hormetic response will occur or not. This has been intensely studied in the area of anxiotytic drug development. In these investigations, researchers have systematically assessed the presence or absence of an hormetic dose response for each of a large number of highly related chemicals, differing by a single molecular characteristic in a long series of agents. These investigations demonstrated that the hormetic biphasic dose response was reproducibly inducible, but it was highly dependent on certain structural characteristics. These hormetic dose responses have the potential to be predicted via SAR methods.[78-80]

Hormesis and avoiding side effects

Hormesis is a biphasic dose response that often results from the actions of partial agonists and partial antagonists. Part agonists/antagonists are extremely common, being seen in most, if not all, receptor systems. The use of partial agonists/antagonists will diminish the likelihood of adverse effects while creating a broader dose response range over which the response would occur.[78-80] These two features are extremely important for the survival of the individual. One can imagine the survival implications of individuals affected by adverse side effects, ranging from headaches to dizziness, to seeing double, amongst others. A major factor, therefore, in evolutionary success is to minimize undesirable side effects of endogenous agonists. As one can see, with the modern pharmaceutical world, this is not an easy task. However, this could be another critical dimension of hormesis within an evolutionary context.

The hormetic pharmacy

Numerous adaptational-based beneficial responses conform to the hormetic dose response. These responses have the capacity to protect vital organs such as the heart, lungs and brain from a host of damaging stresses/conditions. The hormetic response is also manifested via accelerated healing in various experimental systems.[81] Hormetic responses are also seen with cognitive improvement, in slowing down the onset of various aging processes and in a plethora of neurodegenerative diseases, as well as in reducing susceptibility to a broad spectrum of infectious diseases.[29] Hormesis is also seen in the strengthening of bone, reducing the risks of osteoporosis as well as in treating male sexual dysfunctions and with the capacity to grow hair.[82] Research is now being focused on the next generation of pharmaceuticals called hormetic mimetics. These are endogenous or exogenous agents that activate hormetic adaptively beneficial receptor pathways. It is expected that these agents will be translated into life-enhancing pharmaceuticals.[83] In short, hormetic effects are a central feature of the modern and future pharmacy.

Is science self-correcting and if so, how effective is it?

One of the major revelations of hormetic dose responses is that the scientific community was quick to accept the threshold dose-response model and to incorporate it into the entire spectrum of governmental hazard assessment evaluations and in the risk assessment process. The research and regulatory communities accepted its intellectual framework without validating whether this model could accurately predict responses in the low-dose zone. Since homeopathy and what we now call 'traditional' medicine have been engaged in a bitter conflict for nearly 2 centuries, the hormetic dose-response concept became collateral damage in this social, economic and medical battle.[4] This failure to vet the threshold model was largely a consequence of the conflict between homeopathy and traditional medicine. The field of pharmacology, being an important dimension of traditional medicine, aggressively attacked the writings of Hugo Schulz who had proposed that the hormetic biphasic dose response provided the explanatory principle of homeopathy. Since toxicology emerged from pharmacology, it adopted the dose response perspective of its parent, without much self-initiated investigation. The entire experimental, evaluatory, regulatory and teaching aspects of toxicology came to adopt this 1930s mantra of the dose response. The system surprisingly was never critical of its assumptions about the threshold dose response but always found ways to marginalize the hormesis concept. This is even the situation today, especially as manifested by directions of grant programs that control many professional activities. Furthermore, governmental regulatory agencies continue to find the hormetic dose response extremely challenging and threatening, even though it should help them perform their jobs of serving the public considerably better.

Of particular concern is that the research community, especially in the toxicology domain, can have their intellectual climate directed by regulatory agency toxicology needs. Thus, those persons who control grant funding will largely control the creative directions of the research community. In this way, the non-critical acceptance of the threshold dose-response model has been perpetuated through several generations of pharmacologists and toxicologists, who have simply accepted the assumptions of the handed down threshold dose-response model as being correct. The results of such toxicological intellectual indoctrination have led to the present state of affairs. While progress is being made on changing this perspective, there are also strong governmental institutional controls over how one should think about the dose response and the ability to discuss and assess it openly. This leads back to the question, is science self

correcting? Under normal situation, science is efficiently self-correcting with the best ideas eventually emerging. However, when regulatory agencies control the intellectual agenda and funding, the self-correcting nature of science is undermined as we had seen over the past nearly 80 years when it comes to the critical issue of the dose response.

Discussion

In the late 1980s, there was strong interest in determining whether hormesis was a real biological phenomenon or simply a statistical anomaly. Even the first conference on radiation hormesis in 1985 (see Health Physics, 1987 vol. 52, issue 5 for the peer-reviewed conference proceedings) failed to resolve the issue as reflected in a subsequent debate on the topic in the journal *Science* in 1989 by two of the conference leaders.[84,85] However, the opportunity to more systematically assess the hormetic hypothesis dramatically improved with the creation of the hormesis database,[10,11,13] which has collected and assessed over 8000 examples of dose responses displaying evidence of hormetic dose responses. The database permitted an assessment of questions relating to reproducibility of findings, generalizability across biological models, endpoints and chemical classes, as well as the quantitative features of dose responses and temporal nature of the hormetic response. These initial efforts helped to firmly establish that hormetic responses occurred, were reproducible and not uncommon. Despite this advance, there were other questions, especially those relating to the frequency of hormesis in the toxicological literature and the mechanism or family of mechanisms that could account for hormetic dose responses. With respect to the frequency of hormesis, this was to require the creation of a new hormesis database, one that had a priori entry as well as evaluative criteria. This effort, which involved a separate evaluation of nearly 21,000 articles, revealed the first frequency of hormesis within the toxicological/pharmacological literature, with a value of nearly 40%.[5] Furthermore, there was considerable evidence in the pharmacological literature to account for mechanisms by which direct-acting hormetic dose responses occurred using agonist gradients via receptor subunits to activate stimulatory or inhibitory pathways.[5]

One of the key general observations was that the quantitative features of the hormetic dose response were the same, regardless of the biological system, the endpoint that was measured or the agent that induced it. This was a striking general observation that applied to stimulation of tumor cell proliferation, memory enhancement, immune cell stimulation, plant growth, decreases in anxiety and the broad range of other endpoints reported. These quantitative features of the dose response would occur whether the stimulatory response was of a direct or overcompensatory nature. This suggested strongly that the quantitative features of the hormetic dose response were so widespread and general that it may in fact be a quantitative estimate of biological plasticity independent of species.

While the initial emphasis behind the hormetic reappraisal was environmental risk assessment, the data now indicate that this concept is far more general, impacting any aspect of biology concerned with dose-response relationships. This makes the hormesis concept central to molecular biology as well as pharmacology, toxicology[86] and risk assessment.[87-89]

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